CLINICAL INFECTIOUS DISEASE ARTICLES

Bacteremia Due to Viridans Streptococcus in Neutropenic Patients with Cancer: Clinical Spectrum and Risk Factors

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Between 1988 and 1991, 26 episodes of bacteremia due to viridans streptococci occurred in 25 neutropenic patients undergoing intensive chemotherapy for hematologic malignancies. Complications related to the bacteremia were observed in 10 episodes: unilateral pulmonary infiltrates (4), acute respiratory distress syndrome (ARDS) (4), hypotension (3), and endocarditis (2). All patients with ARDS had received high doses of cytosine arabinoside and had bacteremia due to *Streptococcus mitis*. Death occurred in three patients (12%) but was possibly related to bacteremia in only one case. Case patients who had received prophylaxis with quinolones were compared with matched control patients who received similar prophylaxis but who did not have bacteremia due to viridans streptococci. Multivariate analysis of predisposing factors showed that high doses of cytosine arabinoside ($P = .01$), the presence of mucositis ($P = .02$), and the absence of previous therapy with parenteral antibiotics ($P = .01$) were independent risk factors for the development of viridans streptococcal bacteremia. Of 259 patients who had received quinolone prophylaxis during the study period, 22 (8.5%) developed an episode of viridans streptococcal bacteremia as compared with three episodes (3.7%) in 82 patients who had received a quinolone and penicillin ($P = .07$). However, the latter three episodes were caused by strains with decreased susceptibility to penicillin, thus suggesting that resistance to penicillin might limit the use of this antibiotic as a prophylactic agent in the future.

Viridans streptococci are an increasing cause of bacteremia in neutropenic patients with cancer [1–4]. The clinical course may include adult respiratory distress syndrome (ARDS) and shock that can be fatal. Case-control studies have suggested that oral mucosal lesions are the most probable portal of entry [5–7] for viridans streptococci that cause bacteremia and have identified predisposing factors such as the use of high doses of cytosine arabinoside [6, 8], prophylaxis with quinolones [6], and antacids [7]. However, most of these studies suffered from several methodological problems including a limited number of patients [5], absence of control patients matched for the severity of neutropenia [7], imprecise period of observation for risk factors [5–8], and lack of data on colonization [6–8]. The purpose of the present study was threefold: to review all the cases of viridans streptococcal bacteremia that had occurred at our institution between 1988 and 1991, to assess risk factors in a case-control study with control patients matched for sex, age, underlying disease, duration and severity of neutropenia, and quinolone prophylaxis, and to assess the effect of penicillin added to quinolone prophylaxis on colonization with and bacteremia due to viridans streptococci.

Materials and Methods

Selection Criteria

We reviewed the episodes of viridans streptococcal bacteremia that occurred in adult neutropenic patients hospitalized at the Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland) from January 1988 to December 1991. In this unit, blood for cultures is routinely obtained if the patient's temperature rises above 38°C and also before initiation of any antibiotic therapy. Empirical antimicrobial therapy is initiated in cases of fever, unless the increase in temperature is clearly related to transfer of blood products. The following data were collected for each patient: age, gender, underlying disease, antineoplastic therapy, duration and severity of neutropenia, antibacterial and antifungal prophylaxis, use of antacids, colonization with viridans streptococci, mucocutaneous lesions, serology for herpes simplex virus, time to onset of fever or bacteremia, antiinfective therapy, and clini-

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cal status from the onset of the chemotherapy responsible for the development of neutropenia until discharge or death.

Fever was defined as a temperature of at least 38°C sustained for >2 hours. Profound neutropenia was defined as a granulocyte count of <100 cells/mm^3. In all but five patients, for whom only one set of blood for culture was obtained, the diagnosis of viridans streptococcal bacteremia was established by the presence of two or more sets of blood cultures positive for viridans streptococci.

Clinical Evaluation

ARDS was defined by the occurrence of tachypnea (respiratory rate, >25/min), arterial hypoxemia (arterial oxygen pressure, <60 mm Hg), and bilateral pulmonary infiltrates. Shock was defined as a systolic pressure of <90 mm Hg and oliguria.

Selection of Patients for Case-Control Study

Between 1988 and 1991, 26 episodes of viridans streptococcal bacteremia occurred in 25 neutropenic patients undergoing intensive chemotherapy for hematologic malignancies (one patient had two episodes of bacteremia, each during a different episode of neutropenia). In 22 of these 26 episodes, patients had received a quinolone alone for antibacterial prophylaxis and were selected as case patients for a case-control study evaluating risk factors. For each case patient, one control patient was matched for sex, age ±5 years, underlying neoplasia, antimicrobial prophylaxis, and severity and duration of neutropenia. Control patients did not have bacteremia.

Evaluation of Predisposing Factors

Risk factors were evaluated during a period starting from the onset of chemotherapy until the occurrence of bacteremia for case patients and from the onset of chemotherapy and during a matched period of observation for control patients. Risk factors included all findings that suggested infection, bleeding, or chemotherapy-induced toxicity. Sinusitis was defined by clinical and radiographic signs. Vomiting was defined as several episodes of vomiting that persisted for ≥3 consecutive days. Diarrhea was defined as several daily loose stools that persisted for ≥3 consecutive days. Clinically documented esophagitis was defined as gastric or esophageal pain after exclusion of cardiac ischemia. High doses of cytosine arabinoside were defined as >3 g/m^2 every 12 hours.

Effect of Penicillin on Colonization with Viridans Streptococci

Because of the increasing number of cases of viridans streptococcal bacteremia, since 1989 penicillin has been added to quinolone prophylaxis for certain patients in the frame of a new protocol of antimicrobial prophylaxis. A second case-control study was performed for evaluating the effect of prophylaxis with penicillin on colonization with viridans streptococci. In this second study, the control patients of the first study who were receiving prophylaxis with a quinolone alone were matched with similar neutropenic patients receiving penicillin prophylaxis with a quinolone. The selection criteria were the same as those of the first study.

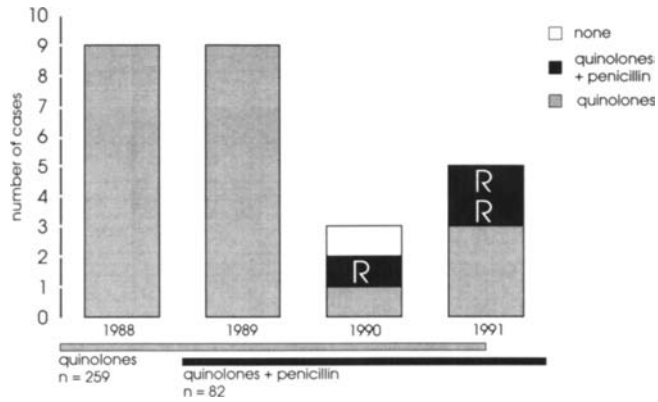

Figure 1. Episodes of viridans streptococcal bacteremia according to the year of occurrence and the type of antibiotic prophylaxis. R = resistant to penicillin (see text).

Microbiology

Specimens of urine and from the nose, mouth/throat, anus, and any suspected area were obtained twice a week for body surveillance cultures. In the presence of fever, specimens of blood and urine and from any suspected site of infection were obtained for culture. Viridans streptococci and the species level were identified according to standard methods [9], and their susceptibility to quinolones and penicillin was assessed by disk diffusion according to the criteria of the NCCLS (National Committee for Clinical Laboratory Standards, 1990) [10].

Statistical Analysis

Differences between categorical variables were tested for significance by the two-tailed Fisher's exact test. A multivariate logistic regression analysis of risk factors was performed with the use of maximal likelihood estimators of the logistic model. A P value of <.05 was considered significant.

Results

Epidemiology

Between 1988 and 1991, 341 episodes of profound neutropenia were observed. Of these episodes, 87 were asso-

ciated with bacteremias, of which 64 (74%) were due to gram-positive cocci; 12 (14%), gram-negative bacilli; 8 (9%), fungi; and 3 (3%), anaerobes. Among the 64 bacteremias due to gram-positive microorganisms, 26 (41%) were caused by viridans streptococci, which were the most prevalent bacteremic organisms (figure 1), accounting for 30% of all bacteremias. The bacteria identified by blood cultures were *Streptococcus mitis* in 15 episodes (58%) and *Streptococcus sanguis* II in 11 (42%). Three of the *S. sanguis* II strains were eventually reclassified as *S. oralis*. For one patient, blood cultures were positive for both *S. sanguis* and *Staphylococcus epidermidis*.

Prophylactic antibacterial agents were a quinolone in 259 episodes of neutropenia and a quinolone and penicillin in 82. Under quinolone prophylaxis, 22 episodes (8.5%) of viridans streptococcal bacteremia were observed as compared with only 3 (3.7%) under prophylaxis with a quinolone and penicillin ($P = .07$). All viridans streptococci isolated from blood cultures were resistant to the quinolone given as prophylaxis. Twenty-two strains (85%) were susceptible to penicillin, two were intermediate, and two were resistant. Three of the patients from whom intermediate or resistant strains were isolated were receiving penicillin prophylaxis at the time of bacteremia. The MICs of penicillin were 0.5, 4, and 4 μg/mL, respectively, for these three patients' strains.

General Characteristics of the Patients

The characteristics of the case patients and their control patients are given in table 1. The median age of the patients in the 26 episodes of bacteremia was 41.3 years (range, 17–76 years), and there were 17 men and 9 women. Fifteen patients (58%) had acute nonlymphocytic leukemia, 5 (19%) had acute lymphocytic leukemia, 2 (8%) had Hodgkin's disease, 2 (8%) had non-Hodgkin's lymphomas, and 2 (8%) had multiple myelomas. Two patients had undergone autologous bone marrow transplantation. Among the 20 patients with leukemia, 2 had received first induction chemotherapy, 7 had received chemotherapy for relapse, and 11 were receiving maintenance chemotherapy. All patients were profoundly neutropenic at the time of bacteremia. The 26 episodes of bacteremia occurred after a median duration of 29.8 days of hospitalization (range, 9–82 days) and 6.4 days (range, 1–12 days) of profound neutropenia.

No patients were receiving parenteral antibiotics when bacteremia occurred, but oral antibacterial prophylaxis had been given to all patients for a median duration of 11.6 days (range, 3–28 days). Prophylaxis consisted of a quinolone in 22 patients (85%) and a quinolone with penicillin in 3 (12%). In one case (4%), prophylaxis with a quinolone was stopped 3 days before the onset of bacteremia because of presumed allergy. The quinolones used were norfloxacin (400 mg bid) in 15 patients (58%), pefloxacin (400 mg bid) in 9 (35%), and ciprofloxacin (500 mg bid) in 1 (4%).

Clinical Conditions Associated with Viridans Streptococcal Bacteremia

At the time of bacteremia, fever was observed in 25 episodes (96%). In the afebrile episode, bacteremia was documented after gastroscopy. Chills were associated with 13 episodes (50%). Four patients developed a rash 1 to 5 days after the bacteremia; drug allergies could not be excluded as the cause of the rash in these patients.

Hypotension. Three patients (12%) had hypotension that was rapidly reversed by volume replacement.

Pulmonary infiltrates. Pulmonary infiltrates were noted in eight episodes (30%). In four episodes (15%), ARDS developed 3 to 4 days after the documentation of bacteremia. Three patients had to be transferred to the intensive care unit. All four patients had received high doses of cytosine arabinoside and had *S. mitis* bacteremia. One episode was due to a penicillin-resistant strain of *S. mitis*. All patients with ARDS recovered. A unilateral pulmonary infiltrate was observed in four episodes (15%), of which two were due to *S. mitis* and two were due to *S. sanguis* II. In one episode, it was present on the day of the onset of bacteremia and was considered as a possible portal of entry. In three episodes, it developed 5, 7, and 8 days after the onset of bacteremia, respectively, and no microorganism was identified in the specimens obtained by bronchoalveolar lavage.

Endocarditis. Two patients developed a new murmur, and at presentation echocardiography revealed findings consistent with endocarditis. One of the patients had had previous valvular abnormalities.

Treatment and Outcome

Initial treatment. All patients were treated with broad-spectrum antibiotics. Initial empirical treatment was found to be appropriate by in vitro susceptibility testing of the bloodstream isolates in all episodes.

Clinical outcome. In 13 episodes (50%), the patients defervesced within the first 4 days of therapy. In nine episodes (35%), defervescence occurred only after 4 days. In four episodes (15%), no clinical response was observed until bone marrow recovery (three episodes) or death (one episode). Three patients (12%) died during the neutropenic episode. In only one patient with uncontrolled leukemia was bacteremia thought to have precipitated death.

Predisposing Factors

Comparison between case patients receiving quinolone prophylaxis and control patients. Table 2 shows the predisposing factors for viridans streptococcal bacteremia. The proportion of case patients colonized with viridans streptococci was higher than that of control patients ($P < .05$). Case patients presented with more mucocutaneous lesions than did

Table 1. General characteristics of neutropenic cancer patients with bacteremia due to viridans streptococcus.

Patient characteristics	Clinical study	Case-control study	
	Episodes (n = 26)	Case patients* (n = 22)	Control patients (n = 22)
Median age in y (range)	41.3 (17–76)	42.9 (17–76)	38.7 (17–74)
Male/female ratio	17/9	13/9	13/9
No. (%) of patients with underlying neoplasia			
Acute leukemia	20 (77)	17 (77)	17 (77)
Lymphoma or myeloma	6 (23)	5 (23)	5 (23)
No. (%) of patients who underwent autologous bone marrow transplantation	2 (8)	1 (4)	1 (4)
Characteristics of neutropenia			
No. (%) of patients with granulocyte counts of $<100/mm^3$	26 (100)	22 (100)	22 (100)
Median duration in d of count $<1,000/mm^3$ (range)	26.1 (10–60)	24.4 (10–60)	27.7 (13–51)
Median duration in d of count $<100/mm^3$ (range)	17.7 (7–43)	16.8 (7–43)	19.9 (4–48)
No. (%) of patients who received oral antifungal prophylaxis	26 (100)	22 (100)	22 (100)
Oral antibacterial prophylaxis			
No. (%) of patients who received quinolones	22 (85)	22 (100)	22 (100)
No. (%) of patients who received quinolones and penicillin	3 (12)	...	...
None	1 (4)†	...	...
Duration in d of therapy (range)	11.6 (3–28)	11.6 (3–28)	12.7 (2–23)

* Patients from the 26 episodes of bacteremia (shown in the first column) who were receiving prophylaxis with a quinolone alone at the onset of bacteremia.

† Quinolone prophylaxis was stopped 3 days before the onset of bacteremia (patient was not selected as a case patient).

control patients (P = .01), especially in the oral cavity. In addition, case patients received high doses of cytosine arabinoside as part of their chemotherapy more often than did control patients (P < .001). Among control patients, 13 (59%) had received antibiotics for empirical treatment of a febrile episode during the matched period of observation. In contrast, among case patients, only one (5%) had received parenteral antibiotics before the onset of bacteremia (P < .001), and this treatment had been stopped 8 days before the onset of bacteremia.

Multivariate analysis of risk factors showed that three factors were independent predictors for the development of viridans streptococcal bacteremia: absence of parenteral antibiotherapy during the observation period (P = .01), high doses of cytosine arabinoside as part of the chemotherapy (P = .01), and the presence of oral mucositis (P = .02).

Effect of Penicillin on Colonization with Viridans Streptococci

Comparison of patients who had received a quinolone alone (control patients for the first case-control study) with matched control patients who had received a quinolone and penicillin revealed that penicillin did not decrease colonization with viridans streptococci (table 3). Colonization at the oropharyngeal site was even higher in patients receiving penicillin (P < .05).

Discussion

Viridans streptococci have become an increasingly common cause of bacteremia in patients undergoing intensive chemotherapy. Recent studies revealed that viridans streptococci were responsible for 14% to 19% of the bacteremias in adult patients with cancer [3, 11]. In our institution, viridans streptococci were responsible for 30% of all bacteremic episodes in neutropenic adults hospitalized from 1988 to 1991 and were the most prevalent cause of bacteremia in this patient population. However, with the addition of penicillin to the quinolone prophylaxis regimen, which has been increasingly prescribed since 1989, a decrease in the incidence of viridans streptococcal bacteremia was observed.

Clinically, most patients presented with only fever and defervesced while receiving broad-spectrum antibiotics. Complications were observed in 10 episodes (38%). In four

Table 2. Predisposing factors for bacteremia.

Patient characteristic	No. (%) with characteristic: Case patients (n = 22)	Control patients (n = 22)	P value (Fisher's exact test)
Body cultures positive for viridans streptococci*	20 (91)	15 (68)	<.05
Nose	3 (14)	0	NS
Oropharyngeal	16 (73)	11 (50)	NS
Perianal	9 (41)	7 (32)	NS
Skin†	1 (5)	1 (5)	NS
Gastrointestinal fluid‡	1 (5)	1 (5)	NS
Mucocutaneous lesions	22 (100)	16 (73)	< .01
Nose (sinusitis or epistaxis)	2 (9)	0	NS
Oropharyngeal	18 (82)	12 (55)	.05
Mucositis	16 (73)	8 (36)	<.05
Gingivitis	6 (27)	3 (14)	NS
Oral candidosis	4 (18)	2 (9)	NS
Dental procedures	0	1 (5)	NS
Perianal	2 (9)	2 (9)	NS
Skin	2 (9)	4 (18)	NS
Gastrointestinal (gastritis or esophagitis)	7 (32)	4 (18)	NS
Other findings			
Pulmonary infiltrate	2 (9)	3 (14)	NS
Rash	8 (36)	5 (23)	NS
Vomiting or diarrhea	9 (41)	5 (23)	NS
Central intravenous catheter	22 (100)	22 (100)	NS
Herpes simplex virus serology (no. positive/no. performed)	13/18 (72)	10/19 (53)	NS
Medications			
High doses of cytosine arabinoside	14 (64)	3 (14)	< .001
Previous parenteral empirical therapy	1 (5)	13 (59)	<.001
Sucralfate	3 (14)	2 (9)	NS
Antacids	5 (23)	3 (14)	NS
H2 antagonists	1 (5)	2 (9)	NS
Corticosteroids	7 (32)	7 (32)	NS
Acyclovir	12 (55)	9 (41)	NS

NOTE. Risk factors were evaluated during a period from the onset of chemotherapy until the occurrence of bacteremia for case patients and from the onset of chemotherapy and during a matched period of neutropenia for control patients. NS = not significant.

* Microbiological data missing for two case patients and one control patient.

† Performed only if lesion was present.

‡ Performed only if endoscopy was performed.

episodes (15%), patients developed ARDS secondary to bacteremia, but none died. A comparable incidence of ARDS was observed by other investigators [3, 7, 12, 13]. The pathophysiological events responsible for the development of ARDS have not been clearly identified. Cytosine arabinoside alone can cause a pulmonary toxic effect resembling ARDS [14, 15]. Thus, it has been suggested that viridans streptococci trigger the development of noncardiogenic pulmonary edema in patients with preexisting damage of the lung due to aggressive cytotoxic treatment [16–18]. This suggestion is in agreement with our study, since all patients who developed ARDS and three of the four patients who developed pulmonary unilateral infiltrates had received high doses of cytosine arabinoside. The species of streptococci might also play a role in the development of ARDS [7]. In the present study, all the patients with ARDS were infected by *S. mitis*, thereby suggesting that this bacteria may be more prone to cause ARDS than the other species of viridans streptococci.

In our series, three patients developed hypotension, but none of the patients had true shock. Two patients developed signs consistent with endocarditis, which has also been reported by other investigators [7].

Only three patients (12%) died during the neutropenic episode. However, bacteremia appeared to play a contributory role in only one death. In other studies, a mortality rate of 11% to 22% has been reported [3, 6, 7].

Three factors were found to predict the occurrence of viridans streptococcal bacteremia. The first factor was the pres-

Table 3. Effect of penicillin prophylaxis on colonization with viridans streptococci.

Patient characteristic	No. (%) with characteristic: Patients treated with a quinolone* (n = 22)	Patients treated with a quinolone and penicillin (n = 22)	P value (Fisher's exact test)
Body site cultures positive for viridans streptococci†	14 (64)	17 (77)	NS
Nose	0	1 (5)	NS
Oropharyngeal	11 (50)	17 (77)	<.05
Perianal	7 (32)	4 (18)	NS
Skin‡	1 (5)	1 (5)	NS
Gastrointestinal fluids§	1 (5)	1 (5)	NS
Mucocutaneous lesions	16 (73)	16 (73)	NS
Nose (sinusitis or epistaxis)	0	2 (9)	NS
Oropharyngeal	12 (55)	15 (68)	NS
Perianal	2 (9)	0	NS
Skin	4 (18)	8 (36)	NS
Gastrointestinal (gastritis or esophagitis)	4 (18)	4 (18)	NS

NOTE. NS = not significant.

* Control patients of the first case-control study.

† Microbiological data missing for one patient treated with quinolone and for two patients treated with quinolone and penicillin.

‡ Performed only if lesion was present.

§ Performed only if endoscopy was performed.

ence of mucositis. Several authors have suggested that oropharyngeal lesions were the most probable portal of entry for viridans streptococci that cause bacteremia [1, 3, 5–7]. This suggestion is consistent with the present case-control study in which a higher rate of oropharyngeal colonization with viridans streptococci was found among patients with bacteremia than among control patients. However, three of our cases suggest that the rest of the digestive tract, particularly the stomach, and the lower respiratory tract might also be occasional portals of entry.

Second, patients with viridans streptococcal bacteremia had significantly more often received high doses of cytosine arabinoside as part of their chemotherapy, thereby confirming results of previous studies [6, 16, 17, 19]. This finding suggests that high doses of cytosine arabinoside may play a role in the development of viridans streptococcal bacteremia. Thus, viridans streptococcal bacteremia may have become more common because of the increasing use of this form of chemotherapy [17].

Third, the absence of parenteral antibiotics during the observation period was another factor significantly associated with the occurrence of viridans streptococcal bacteremia. Thus, broad-spectrum antibiotics prescribed early in the course of the neutropenic episode of the control patients for empirical treatment of a fever probably protected them from viridans streptococcal bacteremia. Indeed, viridans streptococcal bacteremia was found to occur only after a median duration of 6.4 days of profound neutropenia. Since many neutropenic patients develop a febrile episode earlier in the course of neutropenia, they receive parenteral broad-spectrum antibiotics for empirical treatment. In the present study, such treatment was received by 59% of the control patients during the matched period of observation. It is unlikely that the febrile episodes observed in control patients were related to undiagnosed viridans streptococcal bacteremia since blood for cultures is routinely obtained in cases of fever.

Because of their effectiveness in preventing infections due to gram-negative organisms, the fluoroquinolones are frequently used as prophylaxis for patients with cancer. Viridans streptococci are typically resistant to these antibiotics [20, 21], and bacteremia due to these microorganisms has been observed under this prophylactic regimen [1, 2, 6–8, 22].

The above-mentioned reasons are why since 1989 penicillin has been added to quinolones in the prophylactic regimen of some patients in the frame of a new protocol of antimicrobial prophylaxis. This addition resulted in the progressive decrease in the number of cases of viridans streptococcal bacteremia observed in our institution. However, three cases were observed while the patients were receiving prophylaxis with a quinolone and penicillin. In all three cases, the strains were relatively resistant to penicillin. When patients receiving a quinolone alone were compared with matched patients receiving a quinolone with penicillin, no difference was found in the incidence of colonization with viridans strepto-

cocci, thus suggesting that penicillin prevents viridans streptococcal bacteremia but not colonization with viridans streptococci. Therefore, wide and prolonged use of penicillin may induce the development of resistance in a patient and possibly in the community, which could affect the efficacy of penicillin prophylaxis as suggested by the three patients who developed viridans streptococcal bacteremia while receiving a quinolone and penicillin.

In conclusion, viridans streptococci have been an increasing problem in neutropenic patients. This problem is probably related to the use of quinolones as antibacterial prophylaxis [1, 2, 6–8, 22]. Our study has identified the use of high doses of cytosine arabinoside, the presence of mucositis, and the absence of previous parenteral antibiotics as risk factors for the development of viridans streptococcal bacteremia. The adjunction of penicillin to a quinolone as a prophylactic agent appears to confer protection against viridans streptococci bacteremia but does not prevent colonization with the organisms. Therefore, penicillin might select for resistant strains and become ineffective in a given patient or patient population.

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